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Original article

Identification of ELOVL3 as a Novel Prognostic Marker for Liver Cancer

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SUMMARY

Introduction. The incidence of liver cancer is increasing globally. Fatty acids in lipid metabolism are associated with cancer risk by maintaining cancer cell membrane structure and transducing cancer signaling, and their increased synthesis promotes tumor growth, angiogenesis, and tumor metastasis.
Methods. After identification of the ELOVL3 gene involved in fatty acid metabolism, which is related to the prognosis of liver cancer, its expression level was extracted from The Cancer Genome Atlas (TCGA) database, and differential analysis, survival analysis, clinical correlation analysis and nomogram were used to predict the survival rate. A comprehensive meta-analysis was performed to further evaluate the prognostic value of ELOVL3. Finally, enrichment analysis and immune analysis were performed on the high and low expression groups of ELOVL3 gene to explore the value of ELOVL3 in predicting the prognosis and immunotherapy of liver cancer patients.
Results. Patients with high ELOVL3 expression had poor overall survival and progression-free survival. The nomogram and the area under the ROC curve also indicated that the expression of ELOVL3 gene had high accuracy in predicting the survival time of liver cancer patients. The expression of ELOVL3 was significantly different in the early stage of tumor grade, tumor stage and T stage. Enrichment analysis and immunological analysis revealed a variety of information. The immunotherapy analysis also showed that low ELOVL3 was more effective than high ELOVL3 when receiving immunotherapy.
Conclusion. The expression of ELOVL3 gene is significantly elevated in HCC and is associated with cancer development and poor prognosis.

Keywords: **ELOVL3, liver cancer, immunity, biomarkers**

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FOREWORD

At present, the incidence of liver cancer is on the rise worldwide, and it is the sixth most common cancer in the world, which seriously threatens people's health (1). Because of its insidious onset, most patients with liver cancer are already in the advanced stage when they are first diagnosed. The survival time is often less than one year and prognosis is extremely poor (2, 3). Therefore, improving the overall treatment level of liver cancer focuses on early diagnosis and early treatment. At present, alpha-fetoprotein (AFP) is mainly used in clinical practice as a biomarker for early diagnosis of liver cancer. However, the auxiliary diagnosis of alpha-fetoprotein has a high false positive rate and false negative rate, which makes it temporarily unable to meet the clinical requirements (4 - 6). Therefore, finding novel liver cancer markers with high sensitivity and specificity has become one of the main tasks of current research. Tumor is a metabolic disease that restricts the immune response by affecting the microenvironment of cells through abnormal metabolism. The tumor microenvironment plays an important role in the process of tumor proliferation, angiogenesis, invasion, migration and drug resistance by altering cellular gene mutations. Therefore, interventions targeting the tumor microenvironment have been the focus of tumor research in recent years (7). Previous studies have reported that amino acids are important metabolites of immune cells and tumor cells in the tumor microenvironment, and tumor cells can use amino acids for their proliferation, invasion, and immune escape. The metabolic balance of amino acids between immune cells and tumor cells can directly affect the immune status of the tumor microenvironment (8). In addition to amino acids, abnormal changes in metabolic signals, lipid transporters, metabolic substrates, metabolic enzymes and metabolites during lipid metabolism are also considered to be one of the characteristics of malignant tumors and are closely related to anti-tumor immune responses. Abnormal accumulation of lipids in the tumor microenvironment can affect the phenotype and function of immune cells in tumors, leading to immune escape of tumor cells by forming an immunosuppressive tumor microenvironment (9, 10).

Fatty acids are an important energy source and structural component of cells in most species, and their dysregulation can lead to diseases such as arteriosclerosis, diabetes, and fatty liver. In addition, fatty acids are associated with cancer risk by maintaining the structure of cancer cell membranes and transducing cancer signaling (11 - 13). Meanwhile, increased fatty acid synthesis can promote tumor growth, angiogenesis, and tumor metastasis, and is one of the most obvious metabolic changes in tumor cells. Lipid metabolism is one of the key metabolisms in tumor progression, and fatty acid synthase (FASN) is a key lipogenic enzyme that is overexpressed in a variety of human cancers (14). Studies have reported that fatty acid synthase levels and fatty acids are expressed in gastric cancer (15), liver cancer (16), lung cancer (17), prostate cancer (18, 19), breast cancer (20), and pancreatic cancer (21). The purpose of this study was to screen out the fatty acid metabolism genes related to the prognosis of liver cancer, select the target ELOVL3 gene, extract its expression from the TCGA database, conduct differential analysis, survival analysis, clinical correlation analysis, to draw a nomogram to predict its survival rate, and to perform a comprehensive meta-analysis to further evaluate the prognostic value of ELOVL3 using data from two public databases. Finally, enrichment analysis and immune analysis were performed on the high and low ELOVL3 gene expression groups. The value of ELOVL3 in predicting the prognosis and immunotherapy of patients with liver cancer was explored.

MATERIAL AND METHODS

Data sources

In this study, the gene expression (fragments per kilobase, FPKM) and clinically relevant data of liver cancer were downloaded from the TCGA database (https://portal.gdc.cancer.gov/), based on GEO (https://www. ncbi.nlm.nih.gov/geo/) database, to acquire the microarray data profile of GSE76427 of GPL10558. After sorting out the transcriptome data and clinical data and transforming the transcriptome data by ID, we found 309 fatty acid metabolism genes from previous studies (22 - 24) and used the limma package in R studio software to convert the genes in liver cancer. The expression of fatty acid metabolism genes was extracted, and then the differential analysis of fatty acid metabolism genes in liver cancer was performed to find the differential genes and visualize the differential genes. The setting conditions were: logFC filter condition

logFCfilter = 2, fdr filter condition fdrFilter = 0.05. Finally, the differential genes and clinically relevant survival data were merged and the survival package and survminer package in R studio software were used to filter out the genes related to prognosis in the merged data and the significance filter standard coxPfilter = 0.05.

Gene expression and survival analysis

We first explored whether the expression of ELOVL3 in 33 human tumors and normal control tissues was different in the "Diff Exp" module of the website TIMER (http://timer.cistrome.org/). Then, differential analysis and pairwise differential analysis of ELOVL3 in liver cancer were also performed using the "ggpubr", "ggplot2" and "limma" packages in R studio software. Overall survival and progression-free survival between high and low expression groups were assessed in Kaplan-Meier curves and univariate and multivariate independent prognostic analyses were used to determine whether ELOVL3 was independent of other prognostic factors. Then, the ROC curve was drawn to judge the accuracy of the expression of ELOVL3 in predicting the survival time of patients with liver cancer. Finally, predictive nomograms were developed using the "rms", "survival" and "regplot" packages in the R studio software with the expression of clinical features and ELOVL3. Each variable in the nomogram is associated with a score matching which is used to describe the predicted value between the predicted 1-, 3- and 5-year survival events and actual conditions by summing the scores of all variables for each sample to obtain a total score.

META analysis

We searched previous publications in PubMed, Web of Science, and Embase databases for related articles on ELOVL3 expression and liver cancer prognosis. It was found that this study was the first to explore the role of ELOVL3 in the prognosis of HCC, so we collected information from the TCGA and GEO databases to evaluate the correlation between ELOVL3 expression and prognosis in HCC patients. The comprehensive HR and 95% CI were calculated to evaluate the relationship between ELOVL3 expression and the prognosis of patients with liver cancer, and the R language was used for prognostic meta-analysis. If I^2 was greater than 50% and $P > 0.05$, a fixed-effect model was used, otherwise, a random-effects model was used.

Clinical relevance and enrichment analysis of genes

The "limma", "ComplexHeatmap" and "ggpubr" packages in R studio software were used to explore whether the expression of ELOVL3 was different between different clinical groups such as age, gender, tumor stage and tumor grade. Then, according to the expression of ELOVL3, all samples were divided into two groups with high and low expression, and the differential genes in the two groups were searched. The conditions were set to logFCfilter = 1, the fdr filter condition was fdrFilter = 0.05, and the adjusted P value was < 0.05. To further study the differential genes, we also performed GO, GSEA and KKEGG enrichment analysis on the differential genes.

Tumor microenvironment and immune correlation analysis

First, the stromal cell score and immune cell score of each liver cancer case were calculated using the ESTIMATE package in R studio software. Then, the content of immune cells in each liver cancer case and its difference between high and low expression groups were explored. The filter condition of immune cell infiltration results was pFilter = 0.05. The correlation analysis of immune checkpoints was also performed to explore whether ELOVL3 was correlated with immune checkpoint-related genes, and the filter condition of the correlation test p value was set to pFilter = 0.001. Then, the correlation between ELOVL3 gene expression and tumor mutational burden was also explored using "ggplot2", "ggpubr" and "ggExtra" packages in R studio software. Finally, we used http://tcia.at/ to obtain the immune score of liver cancer patients, and then used the "limma" package and "ggpubr" package in R studio software to perform immunotherapy analysis to study the high and low ELOVL3 gene expression groups.

RESULT

Expression and survival analysis of ELOVL3

In this study, we first analyzed the prognostic value of fatty acid metabolism-related genes in 115

liver cancer patients from the HCC cohort (GSE76427). Figure 1A shows five high-risk genes and one low-risk gene. Since there is no previous study on the correlation between ELOVL3 and the prognosis of liver cancer patients and the highest HR value of ELOVL3 gene, this study selected ELOVL3 gene for the follow-up analysis. Pan-cancer analysis using the Tumor Immunity Estimation Resource (TIMER2.0) database found that the expression level of ELOVL3 was significantly up-regulated in 4 cancer types (i.e, ESCA, HNSC, LIHC, and STAD; all $p < 0.01$), while in the other 7 down-regulation was observed in different cancer types (ie, BRCA, KICH, KIRC, KIRP, LUAD, LUSC, PRAD; all $p < 0.01$) (Figure 1B). Next, the individual differential analysis of ELOVL3 in liver cancer better demonstrated its difference between liver cancer tissue and normal tissue. Figure 1C shows that ELOVL3 is up-regulated in liver cancer tissue. The paired differential analysis in Figure 1D also shows that ELOVL3 is different between liver cancer tissue and normal tissue. Survival analysis showed that the survival of patients with high and low expression of ELOVL3 gene had a statistically significant difference, and it was found that patients with high

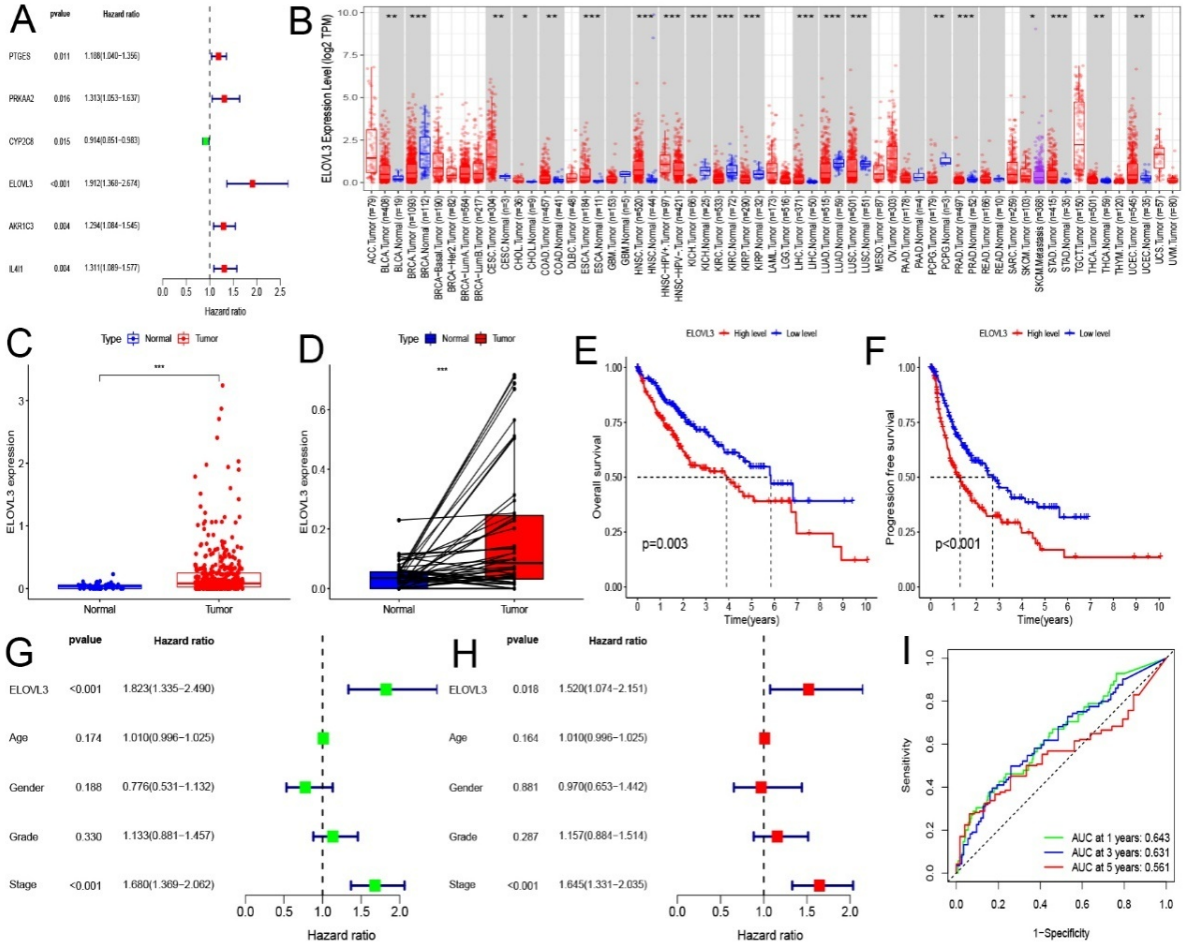

Figure 1. *Screening of genes and their association with prognosis. (A) Fatty acid metabolism-related genes associated with prognosis in HCC patients. (B) Specific expression levels of ELOVL3 in different cancer types and corresponding normal tissues. (C) Differential analysis of ELOVL3 in liver cancer. (D) Paired differential analysis of ELOVL3 in liver cancer. (E, F) Analysis of overall survival and progression-free survival of ELOVL3 in liver cancer. (G, H) Univariate and multivariate independent prognostic analysis of ELOVL3. (I). ROC curves used to predict the 1-, 3-, and 5-year ROC curves in the GSE 76427 set. *p < 0.05, **p < 0.01, ***p < 0.001*

ELOVL3 expression had poorer overall survival and progression-free survival (Figure 1E, Figure 1F). Then, univariate and multivariate independent prognostic analyses were used to explore whether ELOVL3 could act as an independent prognostic factor independent of other clinical traits. Univariate (Figure 1G) and multivariate (Figure 1H) prognostic analyses showed that ELOVL3 had an independent prognosis features. Finally, in Figure 1I, the area under the ROC curve also shows that the expression of ELOVL3 gene predicts that the survival of patients with liver cancer is higher.

META analysis and nomogram

A prognostic meta-analysis was performed using data from 115 HCC patients from GSE76427 and

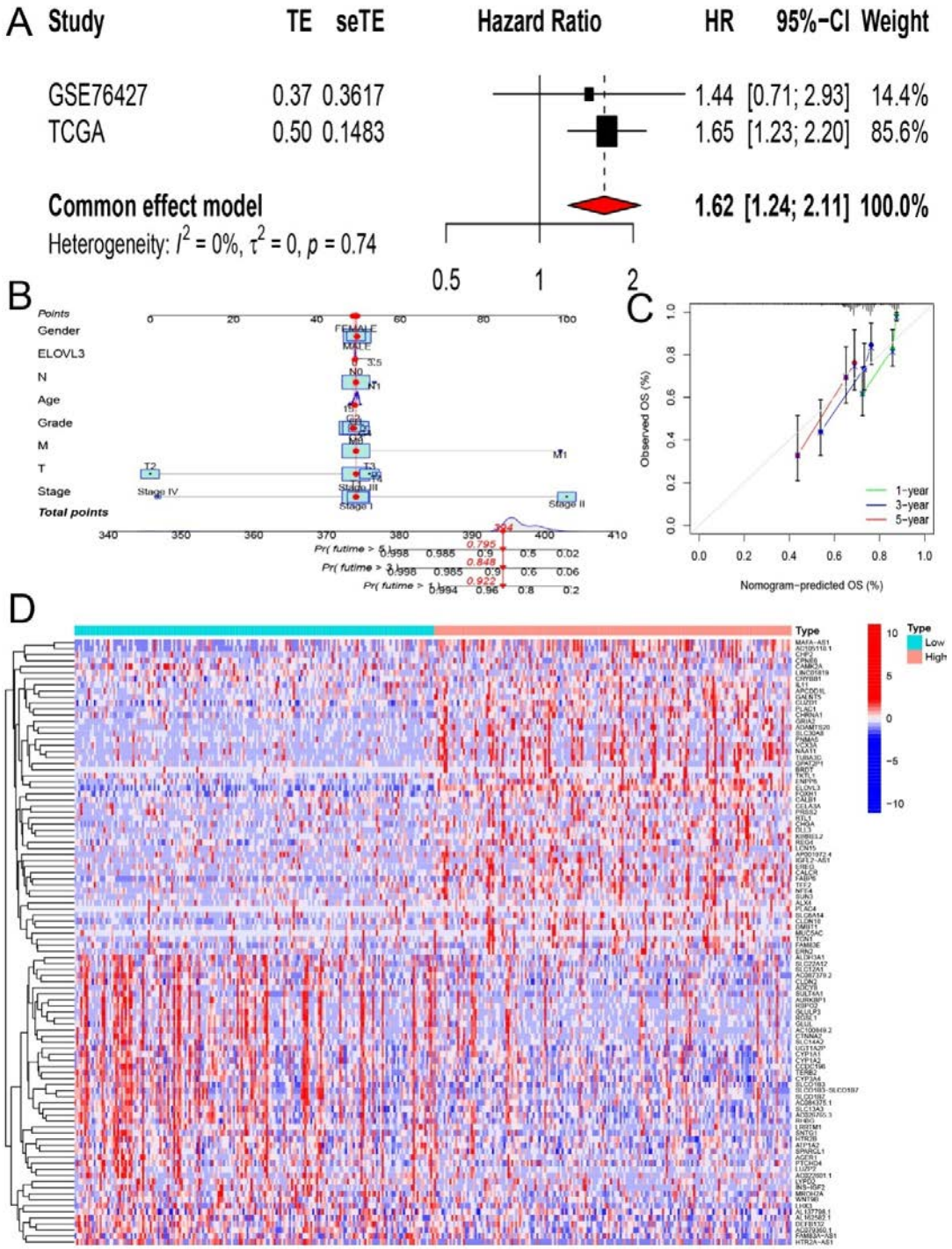

Figure 2. *(A) Forest plot of high ELOVL3 expression from two datasets. (B) Nomogram used to predict 1-, 3-, and 5-year survival in patients with liver cancer. (C) Calibration curves for nomograms used to predict and test 1-, 3-, and 5-year survival in the GSE 76427 dataset. (D). Differential genes in high and low ELOVL3 expression groups*

the TGCA dataset to further explore the impact of ELOVL3 on the prognosis of HCC patients. Figure 2A shows the pooled HR (1.62) and 95% CI (1.24 - 2.11) of the relationship between ELOVL3 gene expression and overall survival, with no significant heterogeneity between the GSE76427 and TCGA datasets. Therefore, it can be well concluded that patients with high ELOVL3 expression can improve the effective prediction of survival of liver cancer patients. Finally, for better clinical application, we constructed a nomogram including ELOVL3 gene expression and clinical parameters to predict the survival rate of liver cancer patients 1, 3, and 5, as shown in Figure 2B. If a patient had a composite score of 394, the survival rate of more than 1 year was 0.922, the survival rate of more than 3 years was 0.848, and the survival rate of more than 5 years was 0.795. At the same time, the calibration curve in Figure 2C also well illustrates the prediction of liver cancer by nomogram. The accuracy of patient survival is high. In Figure 2D, we also divided all liver cancer cases into high and low expression groups according to the expression of ELOVL3 gene, and searched for differential genes in the high and low expression groups for subsequent analysis.

Clinical relevance and enrichment analysis of genes

Various clinical features were used to better understand the prognostic role of ELOVL3. ELOVL3

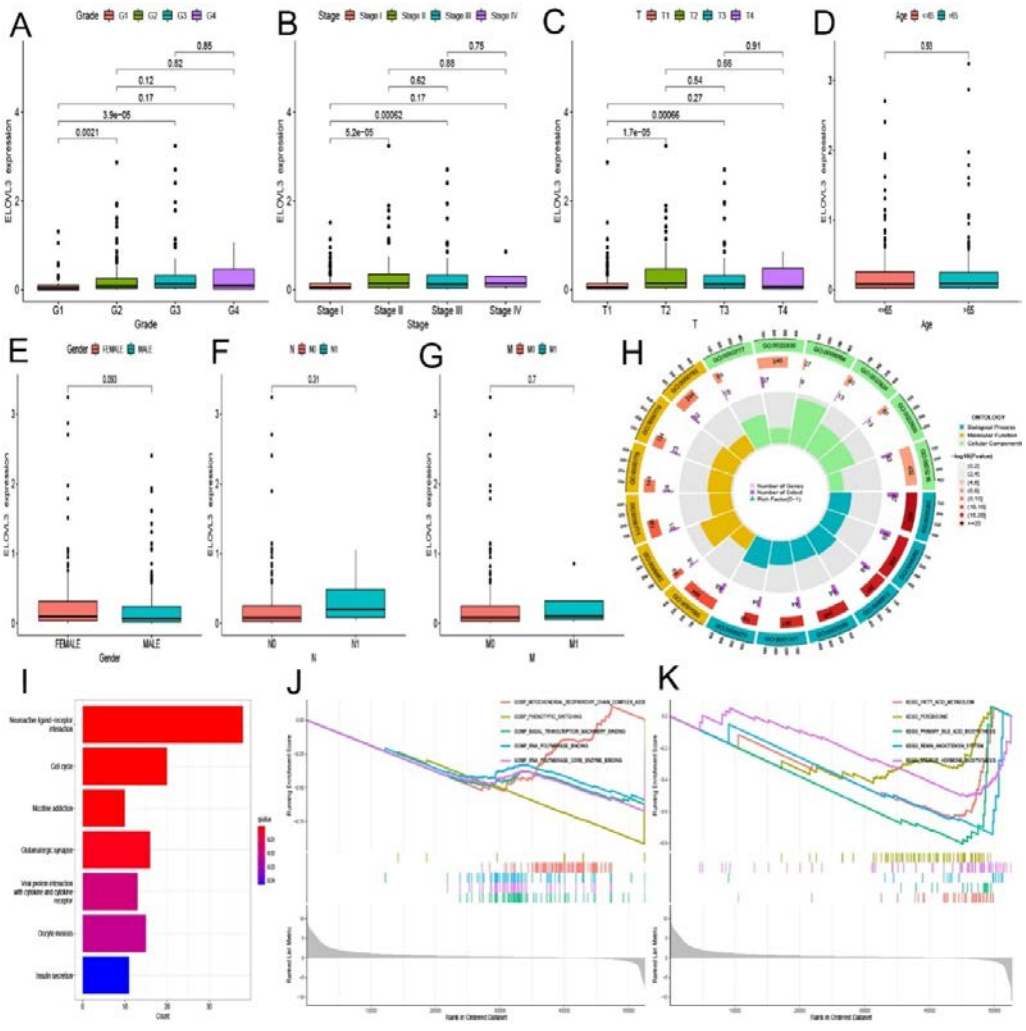

Figure 3. *(A, B, C, D, E, F, G) Correlation analysis of ELOVL3 with tumor grade, tumor stage, T stage, age, gender, N stage and M stage. (H) GO enrichment analysis of differential genes in high and low ELOVL3 expression groups. (I) KEGG enrichment analysis of differential genes. (J) GSEA functional enrichment analysis of differential genes. (K) GSEA pathway enrichment analysis of differential genes*

expression was found in G1, G2 and G3 tumor grade (Figure 3A), in tumor stage 1, 2 and 3 (Figure 3B), and in T1, T2 and T3 of T stage (Figure 3C). Significant statistical differences were found, while no statistically significant differences were found in expression across age (Figure 3D), gender (Figure 3E), N stage (Figure 3F) and M stage (Figure 3G). GO enrichment analysis is presented in Figure 3H. The differential genes in the surface high and low ELOVL3 expression groups were mainly enriched in GO:0048285, GO:0000280, GO:0097060 and GO: 0007059. Figure 3I shows KEGG enrichment analysis of surface differential genes mainly involved in the neuroactive ligand receptor interaction. Mainly in the cell cycle, there were glutamatergic synapses. Next, we also performed GSEA enrichment analysis to explore the functions and pathways active in the high and low ELOVL3 groups. The GSEA function enrichment analysis of Figure 3J shows that the four functions of PHENOTYPIC SWITCHING, BASAL TRANSCRIPTION MACHINERY BINDING, RNA POLYMERASE BINDING and RNA POLYMERASE CORE ENZYME BINDING are highly active in the low expression group of ELOVL3; the pathway enrichment analysis is presented in Figure 3K. It demonstrates that the five pathways of FATTY ACID METABOLISM, PEROXISOME, PRIMARY BILE ACID BIOSYNTHESIS, RENIN ANGIOTENSIN SYSTEM and STEROID HORMONE BIOSYNTHESIS in the low ELOVL3 gene expression group were active.

Tumor microenvironment and immune correlation analysis

To better explore the immune role of ELOVL3, we analyzed the differences in the tumor microenvironment between high and low ELOVL3 expression groups (Figure 4A). Differential analysis of immune cells observed the differences in T cells CD4 memory activated, NK cells resting, and T cells gamma delta between high and low ELOVL3 (Figure 4B). To further study the correlation between ELOVL3 and immune checkpoint-related genes Figure 4C and Figure 4D demonstrate that 5 immune checkpoint-related genes, TNFRSF25, TNFRSF14, PDCD1, TNFRSF18, and CD70 are positively regulated with ELOVL3, which is a future trend. The application of ELOVL3 in immunotherapy provides certain help. In the analysis of tumor mutational burden (Figure 4E), ELOVL3 was positively correlated with tumor mutational burden in HCC patients with significant statistical difference. Finally, we analyzed the effect of immunotherapy in patients with high and low ELOVL3 gene expression groups. The results in Figure 4 (F, G, H, I) show that the effect of low ELOVL3 is better than that of high ELOVL3 when receiving immunotherapy, and the effect of patients in high and low ELOVL3 expression groups when receiving immunotherapy has a significant statistical difference.

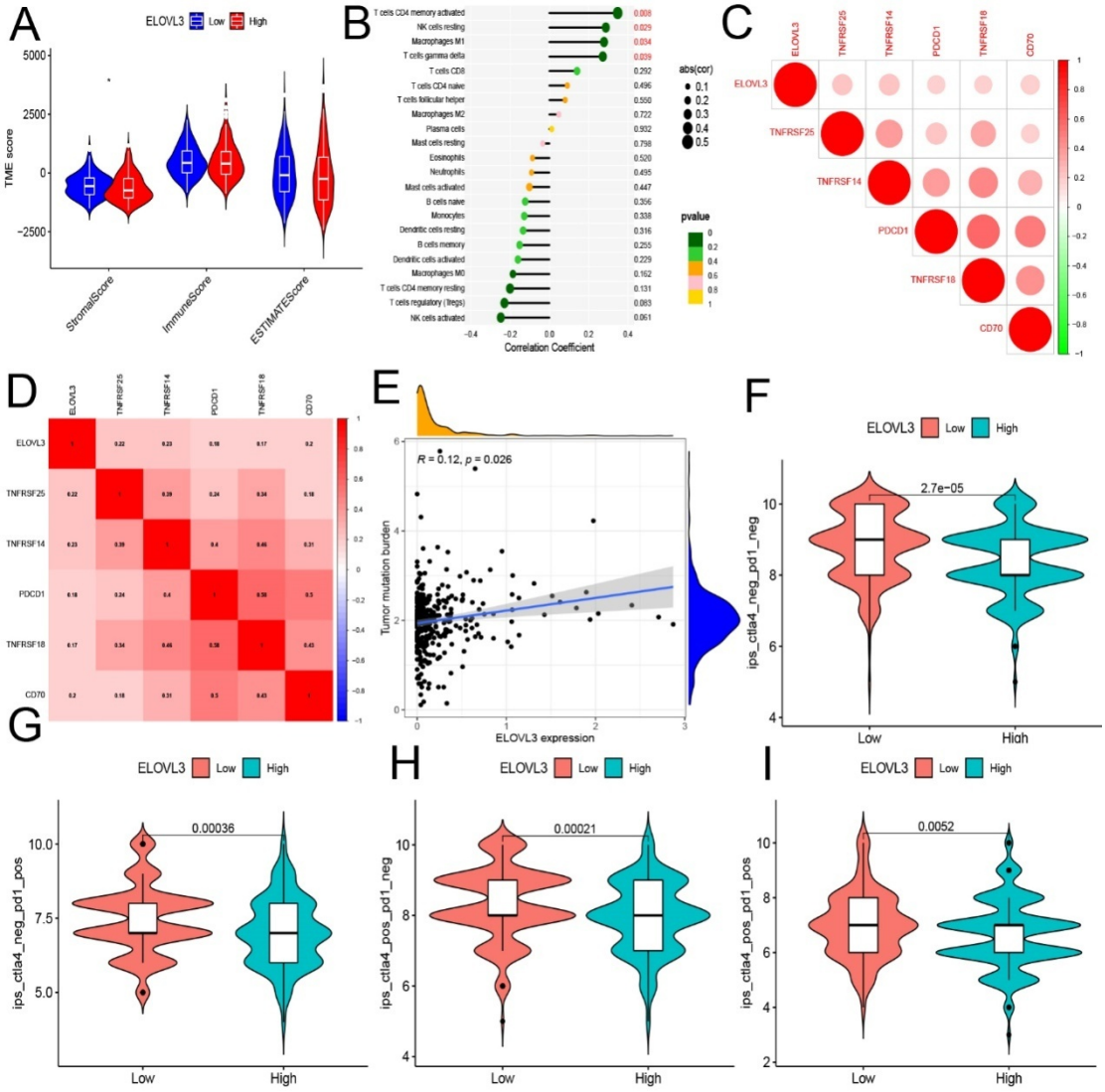

Figure 4. *Tumor microenvironment and immune analysis of ELOVL3. (A) Differential analysis of tumor microenvironment in high and low ELOVL3 expression groups. (B) Differential analysis of immune cells in high and low ELOVL3 expression groups. (C, D) The relationship between immune checkpoint-related genes and ELOVL3. (E) Correlation of ELOVL3 gene expression and tumor mutational burden in HCC patients. (F, G, H, I). Analysis of the effect of immunotherapy in patients with high and low ELOVL3 gene expression groups*

DISCUSSION

The diagnosis of liver cancer mainly depends on the detection of serum tumor markers, imaging and histological examination. As imaging of early liver cancer is not obvious and histological examination is not suitable for the screening of early liver cancer (6, 25), biomarkers have, therefore, become a breakthrough in the early screening of liver cancer. Unfortunately, there is currently no tumor marker that is completely specific for liver cancer in clinical practice. Therefore, finding more sensitive and specific biomarkers for liver cancer is crucial to improve the overall efficacy of patients (4). Very long-chain fatty acid elongation factor 3 (ELOVL3), a member of the Elov1 gene family, is mainly involved in the first-step reaction encoding fatty acids from C16 to long-chain or ultra-long-chain fatty acids (26 - 27). Originally expressed only in liver and brown adipose tissue, a growing number of reports have found that it was also significantly expressed in white adipose tissue and triglyceride glands (28, 29).

In addition, ELOVL3 is also associated with fatty acids and it is also involved in the formation of lipids (30). It has been reported that ELOVL3 promotes the migration and invasion of prostate cancer cells by interacting with the chromatin remodeling protein BRG1 (31). However, research reports on the value of ELOVL3 in liver cancer are rare.

In this paper, through the prognostic value of fatty acid metabolism-related genes in 115 liver cancer patients in the HCC cohort (GSE76427), 6 genes related to the prognosis of liver cancer patients were found: PTGES, PRKAA2, ELOVL3, AKR1C3, IL4I1, CYP2C8. The ELOVL3 gene was selected for analysis. First, pan-cancer analysis found that the expression level of ELOVL3 was significantly up-regulated in 4 cancer types (i.e. ESCA, HNSC, LIHC, and STAD; all $p < 0.01$), while in the other 7 cancer types (i.e. BRCA, KICH, KIRC, KIRP, LUAD, LUSC, PRAD; all $p < 0.01$) it was down-regulated. Then, the individual differential analysis and paired analysis of ELOVL3 in liver cancer well demonstrated the difference between liver cancer tissue and normal tissue. Survival analysis also found that patients with high ELOVL3 expression had worse overall survival and progression-free survival. Univariate and multivariate independent prognostic analysis showed that ELOVL3 could act as an independent prognostic factor, independent of other clinical traits, and the area under the ROC curve also well demonstrated that the expression of ELOVL3 gene predicted higher survival of liver cancer patients. A meta-analysis of the prognostic value of ELOVL3 using data from 115 HCC patients from the GSE76427 and TGCA datasets, pooled HR (1.62) and 95% CI (1.24 - 2.11), was used to clarify the relationship between ELOVL3 gene expression and the overall survival, and there was no significant inhomogeneity between the GSE76427 and TCGA datasets. In addition, we constructed a nomogram to predict the survival rate of HCC patients 1, 3, and 5.

We found that the expression of ELOVL3 was statistically significantly different in early stage in patients with tumor grade, tumor stage, and T stage, while the difference was not statistically significant in the advanced stage. This suggests that ELOVL3 has a higher value in the early diagnosis of liver cancer, and may provide ideas and methods for the early diagnosis of liver cancer in the future. GO enrichment analysis shows that the differential genes of ELOVL3 high expression group and low expression group are mainly enriched in four functions. KEGG enrichment analysis showed that surface differential genes were mainly involved in four pathways: neuroactive ligand receptor interaction, cell cycle, glutamatergic synapse and glutamatergic synapse. Then, GSEA function enrichment analysis showed that the four functions of PHENOTYPIC SWITCHING, BASAL TRANSCRIPTION MACHINERY BINDING, RNA POLYMERASE BINDING and RNA POLYMERASE CORE ENZYME BINDING had strong activity in the low ELOVL3 expression group. The five pathways of METABOLISM, PEROXISOME, PRIMARY BILE ACID BIOSYNTHESIS, RENIN ANGIOTENSIN SYSTEM and STEROID HORMONE BIOSYNTHESIS were active. The functions and pathways of patients in the high ELOVL3 expression group showed a depressed state, which requires more follow-up studies to explore the functional mechanism of ELOVL3. The difference analysis of tumor microenvironment showed that the difference of StromalScore between high and low expression groups was statistically significant. Differential analysis of immune cells observed differences in activated CD4 T cells, resting NK cells, and gamma delta T cells between high and low ELOVL3. Five immune checkpoint-related genes, TNFRSF25, TNFRSF14, PDCD1, TNFRSF18, and CD70 are positively regulated by ELOVL3. The discovery of these immune checkpoint-related genes may provide some help for the application of ELOVL3 in immunotherapy in the future. In the analysis of tumor mutation burden, it was found that ELOVL3 was positively correlated with tumor mutation burden in patients with liver cancer, and there was a significant sta-tistical difference, indicating that ELOVL3 plays a certain role in the tumor microenvironment, but the exploration of these roles and mechanisms requires more research in the future and experiments to supplement the current knowledge. Finally, our analysis of the effect of immunotherapy on patients in the high and low ELOVL3 gene expression group shows that the effect of low ELOVL3 on immunotherapy is better than that of high ELOVL3, and there was a statistically significant difference in the effect of immunotherapy between the ELOVL3 high expression group and the low expression group. Inevitably, there are flaws in this study. First, we have not performed *in vitro* and *in vivo* analyses to explore the relevant functions of ELOVL3 in the progression of HCC tissues. Second, although this study explored the biology of ELOVL3 in HCC through enrichment analysis, the mechanism

linking ELOVL3 expression with HCC development requires more analysis and experimental validation.

CONCLUSION

Our findings suggest that ELOVL3 gene expression is significantly elevated in HCC and is associated with cancer development and poor prognosis. These findings suggest that ELOVL3 may be an oncogene for HCC pathogenesis and progression. The discovery of ELOVL3 may be a new biomarker for early diagnosis and prognosis, and may be a potential new therapeutic target for liver cancer.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository and accession number(s) can be found in the article.

DECLARATIONS

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Peking University Shenzhen Hospital.

Consent for publication

Not applicable

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Identifikacija gena ELOVL3 kao novog prognostičkog markera za karcinom jetre

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S A Ž E T A K

Uvod. Incidencija karcinoma jetre je u globalnom porastu. Masne kiseline su u metabolizmu masti povezane sa rizikom od karcinoma tako što održavaju strukturu membrane ćelija karcinoma i prenošenje tumorskih signala, a njihova povećana sinteza potpomaže rast tumora, angiogenezu i metastaze tumora.
Metode. Nakon identifikacije gena ELOVL3 za metabolizam masnih kiselina, povezanog i sa prognozom karcinoma jetre, njegov nivo ekspresije preuzet je iz *The Cancer Genome Atlas* (TCGA) baze, a za predviđanje stope preživljavanja korišćene su diferencijalna analiza, analiza preživljavanja, analiza kliničke korelacije, kao i normogram. Urađena je opsežna metaanaliza kako bi se dalje procenjivala prognostička vrednost gena ELOVL3. Na kraju je urađena sveobuhvatna genska i imunološka analiza u grupama bolesnika sa visokom i niskom ekspresijom ELOVL3 gena kako bi se ispitala njegova vrednost u predviđanju prognoze i imunoterapije bolesnika sa karcinomom jetre.
Rezultati. Kod bolesnika sa visokom ekspresijom ELOVL3 gena zabeleženi su niska ukupna stopa preživljavanja i preživljavanje bez progesije bolesti. Nomogram i deo grafikona ispod ROC krivulje ukazali su0 na to da je ekspresija ELOVL3 gena imala visoku tačnost u predviđanju perioda preživljavanja bolesnika sa karcinomom jetre. Ekspresija ELOVL3 gena značajno se razlikovala u ranoj fazi tumorskog stepena, stadijumu tumora, kao i T stadijumu. Sveobuhvatna genska analiza i imunološka analiza otkrile su velik broj informacija. Analiza imunoterapije pokazala je da je nizak nivo ELOVL3 gena bio efikasniji od visokog nivoa gena ELOVL3 kod primanja imunoterapije.
Zaključak. Ekspresija ELOVL3 gena značajno je povećana kod HCC-a i povezana je sa razvojem karcinoma i lošom prognozom.

Ključne reči: **ELOVL3, karcinom jetre, imunitet, biomarkeri**